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3825/76

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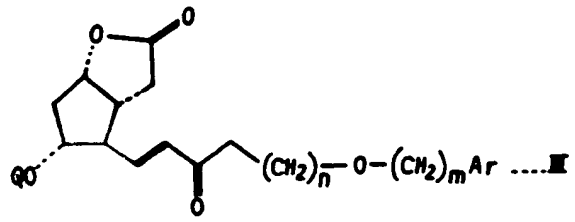
(19)

(54) DERIVATIVES OF CYCLOPENTANEACETIC ACID

(71) We, PFIZER INC. a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to intermediates useful in the preparation of certain novel analogs of the naturally occurring prostaglandins. In particular it relates to intermediates useful in the preparation of novel 16, 17, 18, 19, 20 pentanorprostaglandins, said compounds being described in Patent Application No. 51758/73. (Serial No. 1,456,512).

Generally, this present invention comprises a compound of the formula:



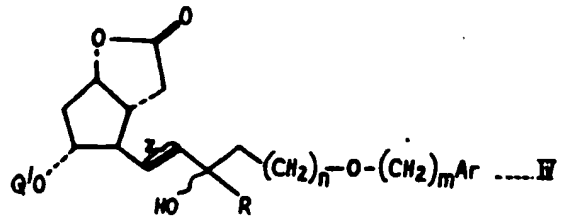
wherein

Ar is phenyl; 3,4-dimethoxyphenyl; 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or monosubstituted phenyl wherein said substituent is halogen trifluoromethyl, phenyl, lower alkyl or lower alkoxy, wherein lower refers to groups having 1—6 carbon atoms

n and m are each 0 or integers from 1 to 3 with the proviso that the sum of n and m does not exceed 3; and

Q is *p*-biphenylylcarbonyl.

This invention further comprises a compound of the formula:



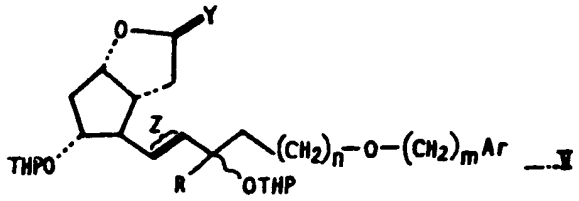
wherein

Ar, m and n are defined above;

R is hydrogen r lower alkyl;

Z is a single bond or a *trans* double bond; and
Q' is hydrogen or *p*-biphenylylcarbonyl, with the proviso that when R and Q' are both hydrogen, Z is a *trans* double bond, N is 0 and m is 0, Ar is 3,4-methylenedioxyphenyl, 3,4,5 - trimethoxyphenyl; α- or β - naphthyl or biphenylyl.

Additionally, this invention comprises a compound of the formula:

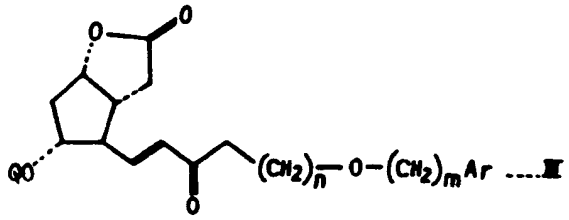


... I

wherein
Ar, R, m and n are as defined hereinbefore:
THP is 2-tetrahydropyranyl;
Z is a single bond or a *trans* double bond; and
Y is O,

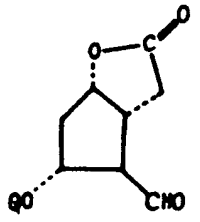
with the proviso that when R is hydrogen, Z is a *trans* double bond, n is 0 and m is 0, Ar is 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or biphenylyl.

Further, the invention is concerned with a process for preparing a compound of the formula:

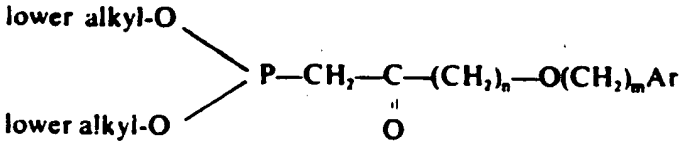


... II

wherein
Ar, m, n and Q are as hereinbefore defined; characterized by reacting a compound of the formula:



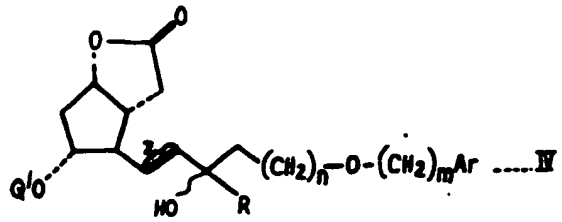
wherein
Q is as defined above with a compound of the formula:



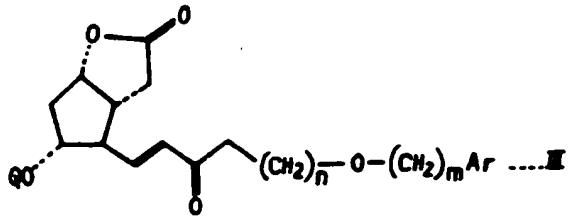
... VI

wherein
m, n and Ar are as defined above.

The invention also provides a process f r preparing a compound of the structure:

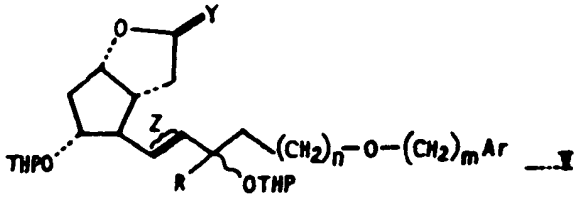


wherein
Ar, R, m, n and Q' are as hereinbefore defined;
characterized by
a) reducing a compound of the Formula III:

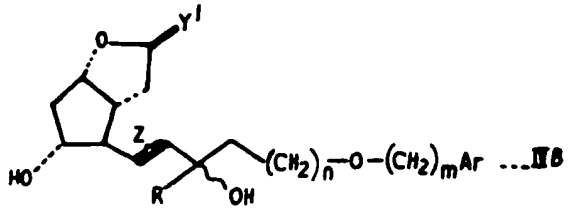


wherein
Ar, n, m and Q are as defined above to afford a compound of Formula IV, above wherein Ar, n and Q are as defined above and R is hydrogen, and, if desired, separating the α- and β-isomers;
b) treating a compound of Formula III, as defined above, with the appropriate metal alkyl to afford a compound of Formula IV, wherein Ar, m, n and Q' are as defined above and R is lower alkyl;
and, if desired, treating a compound of Formula IV, above, wherein Ar, n and R are as defined above and Q' is biphenylylcarbonyl with K_2CO_3 to afford a compound of Formula IV wherein Q' is hydrogen; and, if desired, separating the α- and β-isomers.

Additionally, the invention is concerned with a process for preparing a compound of the formula:—

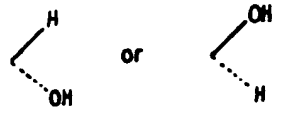


wherein
Ar, R, n, m, Z, Y and THP are as hereinbefore defined;
characterized by
a) reacting a compound of the Formula IVB:



wherein
Ar, R, m, n and Z are as defined above and Y' is O, with 2,3-dihydropyran in the presence of an acid catalyst to afford a compound of Formula V wherein Ar, R, m, n and Z are as defined above and Y is O:

b) reacting a compound of F rmula V, above, wherein Ar, R, m, n and Z are as defined above and Y is O with diisobutyl-aluminium hydride to aff rd a compound of Formula V wherein Ar, R, m, n and Z are as defined above: and Y is



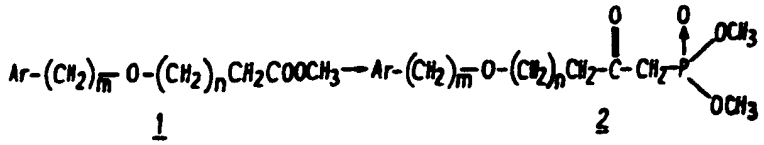
c) by catalytically reducing a compound of Formula IVB above wherein Ar, R, m and n are as defined above, Z is a *trans* double bond and Y' is =O, to afford a compound of Formula V wherein Ar, R, m and n are as defined above, Y is =O and Z is a single bond,

The starting material for the various novel compounds of this invention are available commercially or are made by methods well known to those skilled in the art.

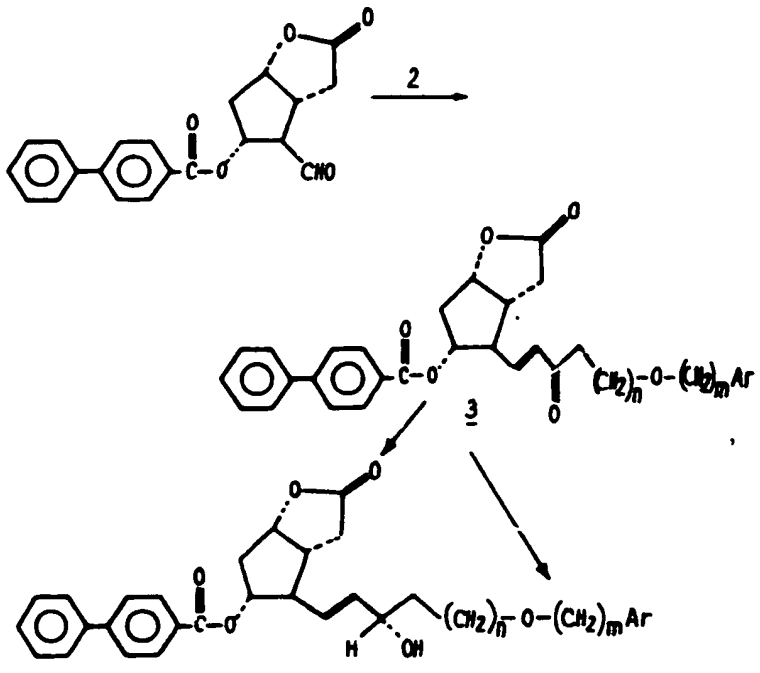
The dialkylphosphonates of formula VI above are described and claimed in Patent Application No. 22858/76 (Serial No. 1,456,514)

The following reaction schemes illustrate the preparation of compounds of this invention.

SCHEME A.

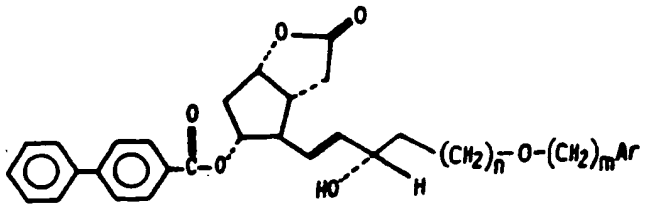


1 2



3 4

SCHEME A (C nt'd).



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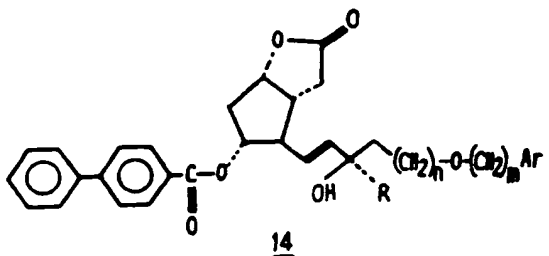

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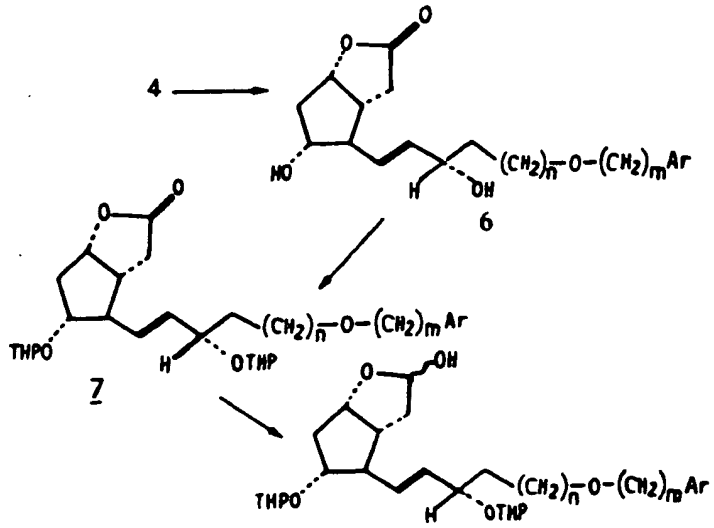
As shown in Scheme A, in *2* → *3* the oxophosphonate *2* obtained as described in Application No. 22858/76 (Serial No. 1,456,514) is reacted with the known [Corey *et al.*, *J. Am. Chem. Soc.*, *93*, 1491 (1971)] aldehyde H to produce, after chromatography or crystallization, the enone *3*.

The enone *3* can be converted to a mixture of tertiary alcohols *13* and *14* by reaction with the appropriate metal alkyl and the isomeric *13* and *14* can be separated by column chromatography. The enone *3* can be reduced with zinc borohydride or with trialkylborohydrides, such as lithium triethylborohydride, to a mixture of alcohols, *4* and *5* which can be separated as above. In this reaction ethers such as tetrahydrofuran or 1,2-dimethoxyethane are usually employed as solvents, although occasionally methanol is preferred to ensure specificity of reduction. Further transformations of *4* are shown on Scheme B.

4 → *6* Is a base catalyzed hydrolysis in which the *p*-biphenylylcarbonyl protecting group is removed. This is most conveniently conducted with potassium carbonate in methanol or methanol-tetrahydrofuran solvent. *6* → *7* Involves the protection of the two free hydroxyl groups with a 2-tetrahydropyranyl group, which can be incorporated in the molecule by treatment with 2,3-dihydropyran and an acid catalyst in an anhydrous medium. The catalyst is usually *p*-toluene-sulfonic acid.

SCHEME B.



7 → *8* Is is a reduction of the lactone *7* to the hemiacetal *8* using diisobutyl aluminium hydride in an inert solvent. Low reaction temperatures are preferred and −60° to −70°C. are usual. However, higher temperature may be employed if

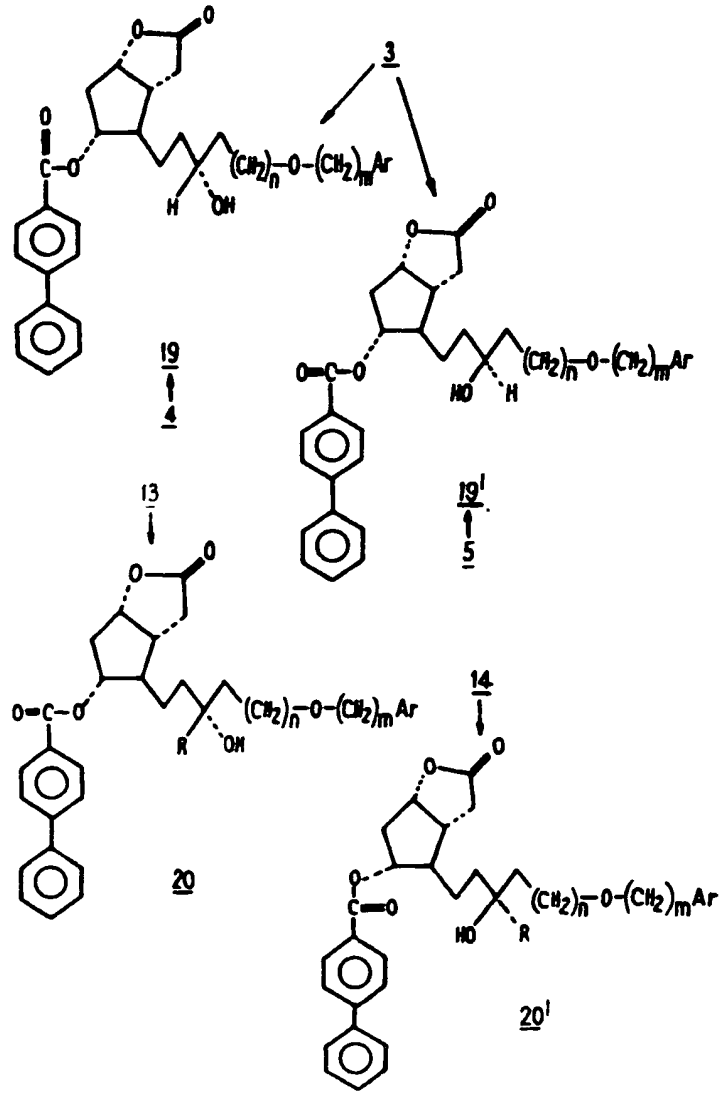
over-reduction does not occur. *8* Is purified, if desired, by column chr matography.

Scheme C illustrates the synthesis of precursors t the 13,14-dihydro-15-substituted-16,17,18,19,20-pentanorprostaglandins.

In *3* → *19* + *19'* the enone *3* is reduced through the use f any of the c mplex metal hydride reducing agents, $LiAlH_4$, $NaBH_4$, KBH_4, $LiBH_4$ and $Zn(BH_4)_2$. Especially preferred is $NaBH_4$. The products *19* and *19'*, are separated from each other by column chromatography.

Furthermore, the compounds *4* and *5* of Scheme A can be reduced catalytically with hydrogen to *19* and *19'*, respectively. The stage at which the double bond is reduced is not critical, and hydrogenation of *6* or *7* of Scheme B will also afford useful intermediates for the 13,14-dihydro prostaglandin analogs of the present invention. This reduction may be achieved with either a homogenous catalyst such as tris-(triphenylphosphine)chlororhodium, or with a heterogeneous catalyst such as platinum, palladium or rhodium. In a similar way the precursors to the 15-lower alkyl-15-substituted-16,17,18,19,20-pentanorprostaglandins are synthesized by substituted compounds *13* and *14* for *4* and *5*, respectively, in the synthetis just described.

SCHEME C.



The following non-limiting Examples illustrate the invention. In these Examples it will be appreciated that all temperatures are expressed in Centigrade, all melting and boiling points are uncorrected.

EXAMPLE I.

2-[3α-*p*-Phenylbenzoyloxy-5α-hydr xy-2β-(3-oxo-4-phenoxy-*trans* - 1 - butenyl) - cyclopent-1α-yl]Acetic Acid, γ-lacton

Dimethyl 2-oxo-3-phenoxypropylphosphonate (5.4 g.), 21 mmole) in 200 ml. anhydrous diethyl ether was treated with 7.9 ml. (19 mm le) 2.5*M* *n*-butyllithium in *n*-hexane (Alfa In rganics, Inc.) in a dry nitrogen atmosphere at room temperature. After 5 min. of stirring, an additional 400 ml. of anhydrous diethyl ether was added followed by 6.0 g. (17 mmole) 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-formylcyclopentan-1α-yl]acetic acid, γ-lactone in one portion and 50 ml. anhydrous diethyl ether. After 35 minutes the reaction mixture was quenched with 5 ml. glacial acetic acid and washed with 100 ml. saturated sodium bicarbonate solution (4×), 100 ml. water (2×), 100 ml. saturated brine (1×), dried ($MgSO_4$) and evaporated to yield 5.2 gm. 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone as a solid after column chromatography (Silica gel, Baker, 60—200 mesh; m.p. 112—114° after crystallization from methylene chloride/hexane.

The ir spectrum (KBr) of the product exhibited absorption bands at 1775 cm^{-1} (strong), 1715 cm^{-1} (strong), 1675 cm^{-1} (medium) and 1630 cm^{-1} (medium) attributable to the carbonyl groups and at 970 cm^{-1} for the *trans* double bond.

EXAMPLE II.

2-[3α-*p*-Phenylbenzoyloxy-5α-hydroxy-2β-(3α-hydroxy-4-phenoxy-*trans*-1 - but - enyl)cyclopent-1α-yl]acetic acid, γ-lactone

To a solution of 5.1 g. (10.5 mmole) 2-[3-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone in 30 ml. dry 1,2-dimethoxyethane in a dry nitrogen atmosphere at ambient temperature was added dropwise 11 ml. (5.5 mmole) of a 0.5*M* zinc borohydride solution. After stirring at room temperature for 2 hours, a saturated sodium bitartrate solution was added dropwise until hydrogen evolution ceased. The reaction mixture was allowed to stir for 5 minutes at which time 250 ml. dry methylene chloride was added. After drying ($MgSO_4$) and concentrating (water aspirator) the resultant semisolid was purified by column chromatography on silica gel (Baker "Analyzed" Reagent 60—200 mesh) using diethyl ether as eluent. After elution of less polar impurities a fraction containing 896 mg. 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3α-hydroxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone, a 600 mg. fraction of mixed *4* and *5* and finally a fraction (1.5 gm.) of 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3β-hydroxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone.

The ir spectrum ($CHCl_3$) of *4* had strong carbonyl absorptions at 1770 and 1715 cm^{-1} and an absorption at 970 cm^{-1} for the *trans* double bond.

EXAMPLE III.

2-[3α,5α-Dihydroxy-2β-(3α-hydroxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α - yl] - acetic acid, γ-lactone

A heterogeneous mixture of 846 mg. (1.7 mmole) of 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3α-hydroxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone, 10 ml. of absolute methanol and 120 mg. of finely powdered, anhydrous potassium carbonate was stirred at room temperature for 20 hours, then cooled to 0°. To the cooled solution was added 1.75 ml. of 1.0*N* aqueous hydrochloric acid. After stirring at 0° for an additional 10 minutes, 10 ml. of water was added with concomitant formation of methyl *p*-phenylbenzoate which was collected by filtration. The filtrate was saturated with solid sodium chloride, extracted with ethyl acetate (4 × 10 ml.), the combined organic extracts were washed with saturated sodium bicarbonate (10 ml.) dried $MgSO_4$) and concentrated to give 445 mg. of viscous, oily 2-[3α,5α-dihydroxy-2β-(3α-hydroxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone.

The ir spectrum ($CHCl_3$) exhibited a strong absorption at 1772 cm^{-1} for the lactone carbonyl and medium absorption at 965 cm^{-1} for the *trans* double bond.

EXAMPLE IV.

2-[5A-Hydroxy-3α-(tetrahydropyran-2-yloxy-2β-(3α-tetrahydropyran - 2 - yloxy - 4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lact ne

To a solution of 445 mg. (1.46 mmole) 2-[3α,5α-dihydr xy-2β-(3α-hydroxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone in 5 ml. anhydrous methylene chloride and 0.4 ml. of 2,3-dihydropyran at 0° in a dry nitrogen

atmosphere was added 5 mg. *p*-t luenesulf nic acid, monohydrate. After stirring for 15 minutes, the r action mixture was combined with 100 ml. diethyl ether, the ethereal solution washed with saturated sodium bicarbonate (1 × 15 ml.) then saturated brine (1 × 15 ml.), dried ($MgSO_4$) and concentrated to yield 752 mg. (>100%) crude 2-[5α-tetrahydr pyran-2-yl xy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone.

The ir ($CHCl_3$) spectrum had a medium absorption at 970 cm^{-1} for the *trans* double bond, and at 1770 cm^{-1} for lactone carbonyl.

EXAMPLE V.

2-[5α-Hydroxy-3α-(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy - 4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetaldehyde, γ-hemiacetal

A solution of 690 mg. (1.46 mmole) 2-[5α-hydroxy-3α-(tetrahydropyran-2-yyloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-phenoxy-*trans*-1-butenyl)cyclopent - 1α-yl]acetic acid, γ-lactone in 8 ml. dry toluene was cooled to −78° in a dry nitrogen atmosphere. To this cooled solution was added 2.0 ml. of 20% by wt. diisobutylaluminium hydride in *n*-hexane (Alfa Inorganics) dropwise at such a rate so that the internal temperature never rose above −65° (15 minutes). After an additional 45 minutes of stirring at −78°, anhydrous methanol was added until gas evolution ceased and the reaction mixture was allowed to warm to room temperature. The reaction mixture was combined with 100 ml. diethyl ether, washed with 50% sodium potassium tartrate solution (4 × 20 ml.), dried (Na_2SO_4) and concentrated to yield 613 mg. 2-[5α-hydroxy-3α-(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-phenoxy-*trans*-1-butenyl)cyclopent - 1 - yl]acetaldehyde, γ-hemiacetal.

EXAMPLE VI.

2-[3α-*p*-Phenylbenzoyloxy-5α-hydroxy-2β-(3-hydroxy-3-methyl-4-phenoxy - *trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone

To a solution of 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone cooled to −78° in diethyl ether-THF, is added dropwise one equivalent of 2*N* solution of methyl lithium in diethyl ether. After stirring at −78° for 15 minutes the reaction is quenched by addition of glacial acetic acid, sufficient to bring pH up to 7. The mixture is diluted with methylene chloride, washed with water, saturated brine, dried (Na_2SO_4) and concentrated to give the oily epimeric alcohols. The crude product is purified by column chromatography on silica gel to give the desired 2-[3α-*p*-phenylbenzyloxy-5α-hydroxy-2β-(3-hydroxy-3-methyl-4-phenoxy-*trans* - 1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone.

EXAMPLE VII.

2-[3α-*p*-Phenylbenzoyloxy-5α-hydroxy-2β-(3α-hydroxy - 4 - phenoxybutyl)cyclo - pent-1α-yl]acetic acid, γ-lactone

A heterogenous solution of 2.5 g. of 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone and 0.25 g. of 5% palladium on charcoal in 30 ml. of absolute methanol is stirred under 1 atmosphere of hydrogen for 4 hours. The mixture is then filtered and concentrated to afford 2-[3A-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxybutyl)cyclopent-1α-yl]acetic acid, γ-lactone.

To a solution of 1.9 g. of the crude hydrogenation product above in 20 ml. of absolute methanol is added excess sodium borohydride and the solution is stirred at room temperature under nitrogen for 2 hours, and then concentrated. The residue is diluted with 0.1*N* hydrochloric acid and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are washed with saturated brine, are dried (Na_2SO_4), and are concentrated. Purificati n of the crude residue by silica gel chromat graphy aff rds 2-[3α-*p*-phenylbenz yloxy-5α-hydroxy-2β-(3α-hydroxy-4-phenoxybutyl)cyclopent-1α-yl]acetic acid, γ-lactone and the 3β-hydroxy epimer.

atmosphere was added 5 mg. *p*-t luenesulfonic acid, monohydrate. After stirring for 15 minutes, the r action mixture was c mbined with 100 ml. diethyl ether, the ethereal solution washed with saturated sodium bicarbonate (1 x 15 ml.) then saturated brine (1 x 15 ml.), dried ($MgSO_4$) and c ncentrated to yield 752 mg. (>100%) crude 2-[5α-tetrahydropyran-2-yloxy-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone.

The ir ($CHCl_3$) spectrum had a medium absorption at 970 cm^{-1} for the *trans* double bond, and at 1770 cm^{-1} for lactone carbonyl.

EXAMPLE V.

2-[5α-Hydroxy-3α-(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy - 4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetaldehyde, γ-hemiacetal

A solution of 690 mg. (1.46 mmole) 2-[5α-hydroxy-3α-(tetrahydropyran-2-yyloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-phenoxy-*trans*-1-butenyl)cyclopent - 1α-yl]acetic acid, γ-lactone in 8 ml. dry toluene was cooled to −78° in a dry nitrogen atmosphere. To this cooled solution was added 2.0 ml. of 20% by wt. diisobutylaluminium hydride in *n*-hexane (Alfa Inorganics) dropwise at such a rate so that the internal temperature never rose above −65° (15 minutes). After an additional 45 minutes of stirring at −78°, anhydrous methanol was added until gas evolution ceased and the reaction mixture was allowed to warm to room temperature. The reaction mixture was combined with 100 ml. diethyl ether, washed with 50% sodium potassium tartrate solution (4 x 20 ml.), dried (Na_2SO_4) and concentrated to yield 613 mg. 2-[5α-hydroxy-3α-(tetrahydropyran-2-yloxy)-2β-(3α-tetrahydropyran-2-yloxy-4-phenoxy-*trans*-1-butenyl)cyclopent - 1 - yl]acetaldehyde, γ-hemiacetal.

EXAMPLE VI.

2-[3α-*p*-Phenylbenzoyloxy-5α-hydroxy-2β-(3-hydroxy-3-methyl-4-phenoxy - *trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone

To a solution of 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone cooled to −78° in diethyl ether-THF, is added dropwise one equivalent of 2*N* solution of methyl lithium in diethyl ether. After stirring at −78° for 15 minutes the reaction is quenched by addition of glacial acetic acid, sufficient to bring pH up to 7. The mixture is diluted with methylene chloride, washed with water, saturated brine, dried (Na_2SO_4) and concentrated to give the oily epimeric alcohols. The crude product is purified by column chromatography on silica gel to give the desired 2-[3α-*p*-phenylbenzyloxy-5α-hydroxy-2β-(3-hydroxy-3-methyl-4-phenoxy-*trans* - 1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone.

EXAMPLE VII.

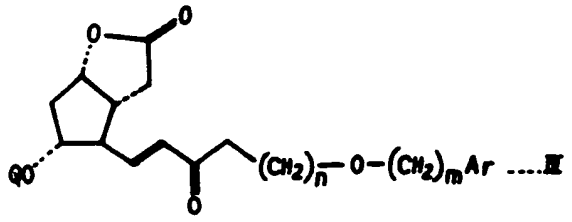
2-[3α-*p*-Phenylbenzoyloxy-5α-hydroxy-2β-(3α-hydroxy - 4 - phenoxybutyl)cyclo - pent-1α-yl]acetic acid, γ-lactone

A heterogenous solution of 2.5 g. of 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxy-*trans*-1-butenyl)cyclopent-1α-yl]acetic acid, γ-lactone and 0.25 g. of 5% palladium on charcoal in 30 ml. of absolute methanol is stirred under 1 atmosphere of hydrogen for 4 hours. The mixture is then filtered and concentrated to afford 2-[3A-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3-oxo-4-phenoxybutyl)cyclopent-1α-yl]acetic acid, γ-lactone.

To a solution of 1.9 g. of the crude hydrogenation product above in 20 ml. of absolute methanol is added excess sodium borohydride and the solution is stirred at room temperature under nitrogen for 2 hours, and then concentrated. The residue is diluted with 0.1*N* hydrochloric acid and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are washed with saturated brine, are dried (Na_2SO_4), and are concentrated. Purification of the crude residue by silica gel chromatography affords 2-[3α-*p*-phenylbenzoyloxy-5α-hydroxy-2β-(3α-hydroxy-4-phenoxybutyl)cyclopent-1α-yl]acetic acid, γ-lactone and the 3β-hydroxy epimer.

WHAT WE CLAIM IS:—

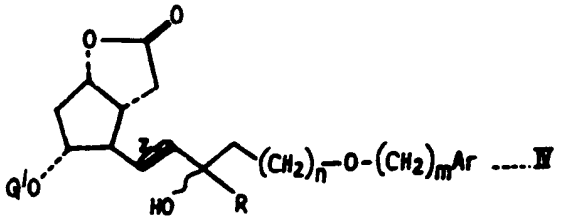
1. A compound of the formula:



wherein

Ar is phenyl; 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or monosubstituted phenyl wherein said substituent is halogen, trifluoromethyl, phenyl, lower alkyl or lower alkoxy; each of n and m is 0 or an integer from 1 to 3 with the proviso that the sum of n and m does not exceed 3; and Q is *p*-biphenylylcarbonyl.

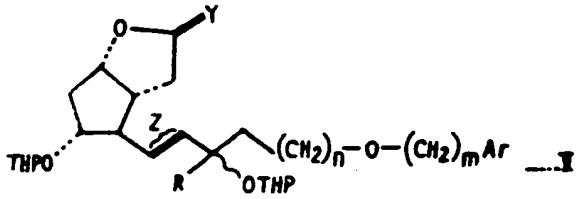
2. A compound of the formula:



wherein

Ar, m and n are as defined in claim 1, Z is a single bond or a *trans* double bond, R is hydrogen or alkyl containing 1 to 6 carbon atoms, and Q' is hydrogen or *p*-biphenylylcarbonyl, with the proviso that when R and Q' are both hydrogen, Z is a *trans* double bond, n is 0 and m is 0, Ar is 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α-or β-naphthyl or biphenylyl.

3. A compound of the formula:

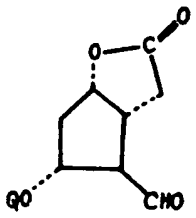


wherein

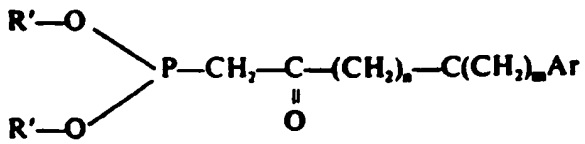
Ar, m and n are as defined in claim 1, R is as defined in claim 2, THP is 2-tetrahydropyranyl, Z is a single bond or *trans* double bond, and Y is 0 or

with the proviso that when R is hydrogen, Z is a *trans* double bond, n is 0 and m is 0, Ar is 3,4-methylenedioxyphenyl; 3,4,5-trimethoxyphenyl; α- or β-naphthyl or biphenylyl.

4. A process for preparing a compound of formula III as claimed in claim 1, which comprises reacting a compound of the formula:



wherein Q is as defined in claim 1 with a compound of the formula:



wherein
Ar, m and n are as defined in claim 1 and R' is an alkyl group containing 1 to 6 carbon atoms.

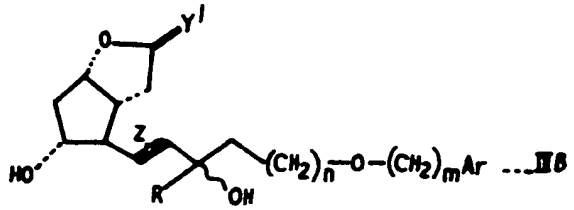
5. A process for preparing a compound of formula IV as claimed in claim 2, which comprises:

(a) reducing a compound of formula III as claimed in claim 1 to afford a compound of formula IV wherein R is hydrogen and, if desired, separating the α- and β-isomers;

(b) treating a compound of formula III as claimed in claim 1 with the appropriate metal alkyl to afford a compound of formula IV wherein R is lower alkyl, and if desired, hydrolysing a compound of formula IV wherein Ar, m, n and R are as defined in claim 2 and Q' is biphenylylcarbonyl with a base to afford a compound of formula IV wherein Q' is hydrogen, and, if desired, separating the α- and β-isomers.

6. A process for preparing a compound of formula V as claimed in claim 3, which comprises:

(a) reacting a compound of the formula:



wherein
Ar, R, m, n and Z are as defined in claim 3 and Y' is =O, with 2,3-dihydropyran in the presence of an acid catalyst to afford a compound of formula V, wherein Ar, R, m, n and Z are as defined in claim 3 and Y is =O;

(b) reacting a compound of formula V, wherein Ar, R, m, n and Z are as defined in claim 3 and Y is=O with diisobutyl aluminium hydride to afford a compound of formula V wherein Ar, R, m, n and Z are as defined in claim 3 and Y is

(c) catalytically hydrogenating a compound of formula IV B as defined in (a) above wherein Z is a *trans* double bond and Y' is =O, to afford a compound of formula V wherein Ar, R, m and n are as defined in claim 3, Y is =O and Z is a single bond.

7. Compounds of formulae III, IV and V as claimed, respectively, in claim 1, 2 and 3, substantially as hereinbefore described with reference to the Examples.

8. Processes as claimed in claims 4 to 6 for preparing compounds of formulae III, IV and V, herein, substantially as hereinbefore described with reference to the Examples.

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